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Palladium-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals.

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Dedication ((optional))

Abstract: Palladium (II) in combination with a monodentate phosphine ligand enables the unprecedented direct and α-stereoselective catalytic synthesis of deoxyglycosides from glycals. Initial mechanistic studies suggest that in the presence of *N*-phenyl-2-(di-tert-butylphosphino)pyrrole as the ligand, the reaction proceeds via an alkoxy-palladium intermediate that increases the proton acidity and oxygen nucleophilicity of the alcohol. The method is exemplified with a wide range of glycal donors and acceptors, including substrates bearing alkene functionalities.

The ability to perform *O*-glycosylation reactions in a catalytic and stereoselective manner is one of the main remaining challenges in carbohydrate chemistry. Biologically relevant chiral acetals such as deoxy-hexoses are prominent components of natural products,[1] and present a significant synthetic challenge because of the lack of substituents at C-2 to direct the nucleophile approach (Scheme 1). Thus, efforts, from our group[2] and others[3] have been devoted to achieve their stereoselective synthesis. Recent years have seen a steady increase in the application of transition metal catalysis to oligosaccharide synthesis,[4] since the careful choice of ligand/transition metal combination can offer significant improvements over traditional methods in terms of atom economy, high yields and control of anomeric selectivity. The palladium-catalyzed direct activation of 1,2-unsaturated glycals to yield the corresponding 2,3-unsaturated Ferrier products with good to excellent selectivities is well established and it is believed to proceed via π-allyl intermediates.[4b, 4c, 5]

Herein we describe the unprecedented Pd-catalysed stereoselective synthesis of deoxyglycosides directly from glycals. Products resulting from addition of the proton and alkoxide nucleophile across the carbon-carbon double bond are formed when monodentate *N*-phenyl-2-(di-tert-butylphosphino)pyrrole is employed as the ligand. This outcome is likely derived from an increase in affinity of palladium towards the OH nucleophile, which allows the reaction to proceed via an alkoxypalladation-type mechanism to yield the glycoside with high α-stereocontrol.

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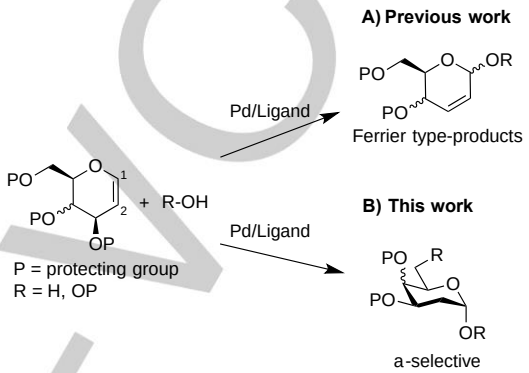
Supporting information for this article is given via a link at the end of the document and includes full experimental and characterization data for all compounds, including NMR spectra.

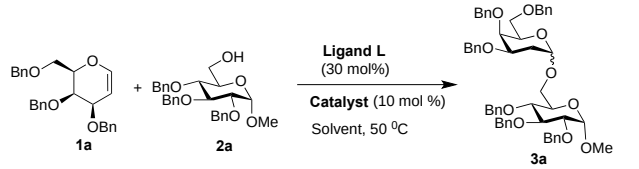


Scheme 1. A) Pd-catalysed synthesis of 2,3-unsaturated glycoside; B) Pd-catalysed synthesis of deoxyglycosides.

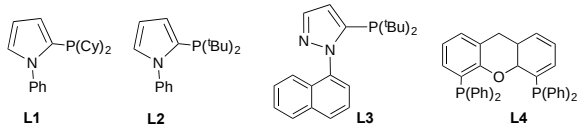
The ligand in a transition metal catalyzed reaction plays a key role in stabilizing and activating the central metal atom and fine-tuning the selectivity of the transformation. Initial experiments began with the screening of a series of commercial mono- and bidentate phosphine ligands **L1-L8 (**30 mol%), for their ability to promote the stereoselective glycosylation of perbenzylated galactal **1a** with glucoside acceptor **2a**[6] in the presence of 10 mol% of $Pd(MeCN)_2Cl_2$ in CH_2Cl_2 at 50 °C. As summarized in Table 1, only monodentate ligands **L1**, **L2** and **L3** with Pd(II) were able to activate the glycal and **3a** was obtained in low to moderate yield (37-75%), with **L2** giving the best α-selectivities (>30:1) (Table 1, entries 2-4). Interestingly, no 2,3-unsaturated Ferrier product was observed in any of the reactions when the phosphine ligand was present, while reactions in the absence of ligand yielded an inseparable mixture of Ferrier and glycoside products. Next, we decided to explore solvent effects, reaction temperature and catalyst loading. The use of acetonitrile or toluene was detrimental to yield (entries 10 and 11), while reaction rate was significantly diminished at room temperature in CH_2Cl_2 (entry 13). Finally, increasing Pd(II) loading to 25 mol% gave optimal yields and α-stereocontrol (90% and >30:1 α□β ratio) within 17 hours (entry 14 *vs* entry 3 (10 mol%) and entry 12 (20 mol%)). To further investigate the effect of the catalyst, a series of different Pd (II) catalysts were also screened in the glycosylation reaction in the presence of **L2** (Table 1, entries 15-19). It was found that removing or replacing the Cl counterion by either a *p*-toluenesulfonate, tetrafluoroborate or trifluoromethane-sulfonate was detrimental to yield, while replacement of acetonitrile with benzonitrile (entry 15) did not affect yield or stereocontrol. It is important to note that reactions with **L2**, in the absence of Pd did not work.

Having established the optimum reaction conditions, our attention then turned to exploring the substrate scope of the coupling reaction between **1a** and a range of OH nucleophiles

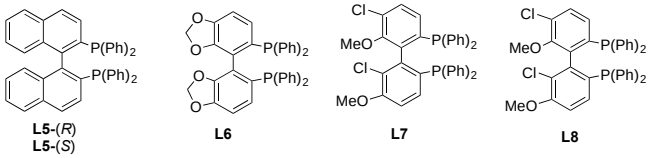
Table 1. Initial catalyst screen in the glycosylation of galactal 2a.



1a 2a 3a



L1 L2 L3 L4



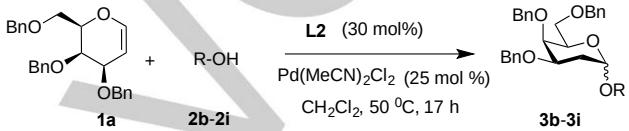
L5-(*R*) L5-(*S*) L6 L7 L8

Entry	Ligand	Catalyst	Time (h)	Solvent	Yield (%)[b]	α:β[b]
1	-	$Pd(MeCN)_2Cl_2$	24	CH_2Cl_2	-[a]	N/A
2	**L1**	$Pd(MeCN)_2Cl_2$	24	CH_2Cl_2	37	14:1
3	**L2**	$Pd(MeCN)_2Cl_2$	24	CH_2Cl_2	75	>30:1
4	**L3**	$Pd(MeCN)_2Cl_2$	24	CH_2Cl_2	45	10:1
5	**L4**	$Pd(MeCN)_2Cl_2$	24	CH_2Cl_2	0	N/A
6	**L5**	$Pd(MeCN)_2Cl_2$	24	CH_2Cl_2	0	N/A
7	**L6**	$Pd(MeCN)_2Cl_2$	24	CH_2Cl_2	0	N/A
8	**L7**	$Pd(MeCN)_2Cl_2$	24	CH_2Cl_2	0	N/A
9	**L8**	$Pd(MeCN)_2Cl_2$	22	CH_2Cl_2	0	N/A
10	**L2**	$Pd(MeCN)_2Cl_2$	24	MeCN	54	25:1
11	**L2**	$Pd(MeCN)_2Cl_2$	24	Toluene	39	>30:1
12	**L2**	$Pd(MeCN)_2Cl_2$	17	CH_2Cl_2	82[c]	>30:1
13	**L2**	$Pd(MeCN)_2Cl_2$	17	CH_2Cl_2	27[c,d]	>30:1
14	**L2**	$Pd(MeCN)_2Cl_2$	17	CH_2Cl_2	90[e]	>30:1
15	**L2**	$Pd(PhCN)_2Cl_2$	17	CH_2Cl_2	86	>30:1
16	**L2**	$Pd(CH_3CN)_2(OTs)_2$	17	CH_2Cl_2	58	>30:1
17	**L2**	$Pd(CH_3CN)_4(OTf)_2$	17	CH_2Cl_2	N/A[f]	N/A
18	**L2**	$Pd(CH_3CN)_4(BF4)_2$	17	CH_2Cl_2	32	>20:1
19	**L2**	$Pd(OAc)_2$	17	CH_2Cl_2	0	N/A
20	**L2**	-	17	CH_2Cl_2	0	N/A

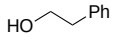
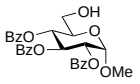
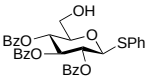
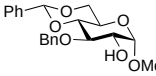
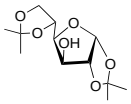
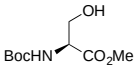
[a]Reactions in the absence of ligand yielded a complex mixture on products. [b] Determined by crude ^{1}H-NMR. [c] Reaction with 20 mol % Pd in CH_2Cl_2 (Isolated yield shown) [d] Reaction at RT. [e] Reaction with 25 mol% Pd in CH_2Cl_2 (Isolated yield shown). [f] Inseparable complex mixture of products.. N/A = not applicable.

2b-**2i** (Table 2). In all cases, reactions proceeded smoothly and in good to excellent yields and α-selectivity, demonstrating that the catalytic system tolerates the presence of common alcohol and amine protecting groups such as acetals, ethers, esters and carbamates. Glycosylations with primary alcohols **2b**-**2d**, thioglycoside **2e** and Boc-protected serine **2h** afforded the corresponding glycoside products in 69-96% yield within 17 h and with an >30:1 α:β ratio to only α (Table 2, entries 1-4 and 7).Similarly, reactions with secondary alcohols such as glycosides **2f** and **2g** or N-hydroxysuccinimide **2i** also afforded the desired products in good yields (73-85 %) and with high α-selectivity (>30:1 α:β ratio to only α) (entries 5, 6 and 8).

Table 2. Acceptor scope in glycosylation reactions with galactal 2a.



1a 2b-2i 3b-3i

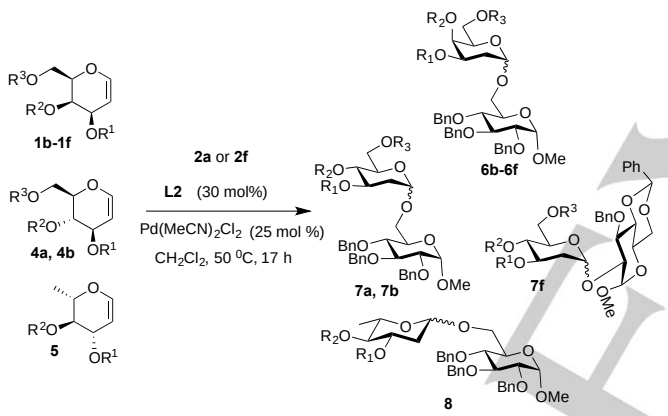
Entry	ROH		Yield (%)[a]	α:β[b]
1		**2b**	69	α only
2	BnOH	**2c**	96	>30:1
3		**2d**	82	>30:1
4		**2e**	84	>30:1
5		**2f**	73	α only
6		**2g**	74	>30:1
7		**2h**	88	α only
8		**2i**	85	α only

[a]Yield of isolated product. [b] Determined by crude ^{1}H-NMR.

To investigate the scope of the glycal donor, a series of differentially protected galactals **1b**-**1f**, glucals **4a** and **4b** and L-rhamnal **5** bearing methyl, acetate, benzyl, silyl ether and siloxane protecting groups were prepared and subjected to the reaction conditions with **2a** (bearing a primary OH) or **2f** (bearing a secondary OH) as nucleophile acceptors (Table 3). Pleasingly, high yields (68-86%) and excellent selectivities for α-linked glycosides (>10:1 to >30:1 α:β ratio) were obtained in all

examples, with the exception of peracetylated galactal **1e** (entry 4). Although we show that ester groups are tolerated elsewhere in the glycal donor (Table 3, entry 1), the presence of a deactivating ester group at C-3 in close proximity to the reacting double bond is known to significantly decrease the reactivity of the donor.[2a, 7] Encouragingly, the reaction was also amenable to glycosylations with glucal substrates, and reactions between 3,4-*O*-siloxane protected **4a**[2c] and **4b**[2c] with primary and secondary OH nucleophiles **2a** or **2f** afforded the corresponding glycosides **7a**, **7b** and **7f**, with high α-stereocontrol (>30:1, α:β to α only) and good yields (68-86 %, entries 6-8). 2,6-Dideoxyglycosides are also an important class of compounds and their stereoselective synthesis is further complicated by the lack of oxygen substituents at both C-2 and C-6.[8] Excitingly, activation of 3,4-*O*-siloxane protected L-rhamnal **5** afforded **8** in 75% yield within 17 h and with a 10:1 α:β ratio (entry 9). These results further highlight that the catalytic system works well across a range of reactivity profiles in both the glycal moiety and nucleophile acceptor.

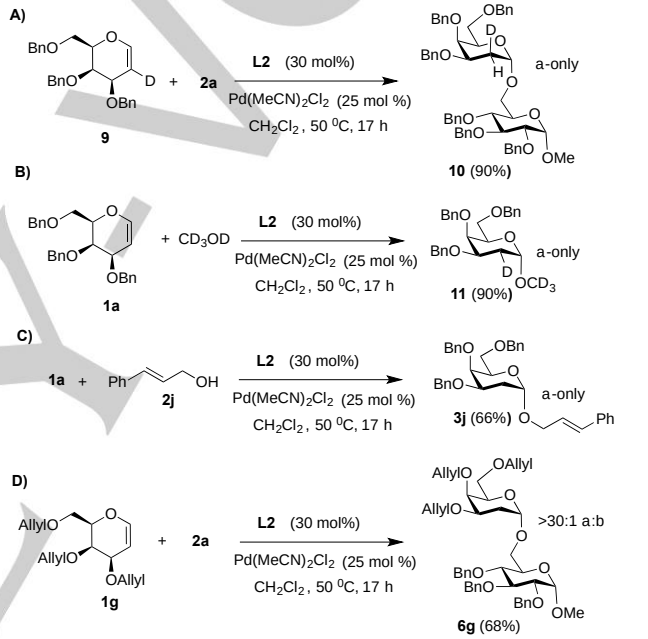
Table 3. Reaction of glycals 1b-1f, 4a, 4b and 5 with model glycosyide acceptors 2a or 2b.



Entry		R^1	R^2	R^3	Product	Yield (%)[a]	α:β[b]
1	**1b**	Bn	Bn	Ac	**6b**	82	>21:1
2	**1c**	TBS	TBS	TBS	**6c**	82	>30:1
3	**1d**	Me	Me	Me	**6d**	78	>30:1
4	**1e**	Ac	Ac	Ac	**6e**	0	N/A
5	**1f**	MOM	MOM	MOM	**6f**	85	>30:1
6	**4a**	O[Si(*i*-Pr)$_2$]$_2$		Bn	**7a**	86	>30:1
7	**4b**	O[Si(*i*-Pr)$_2$]$_2$		TIPS	**7b**	75	>30:1
8	**4b**	O[Si(*i*-Pr)$_2$]$_2$		TIPS	**7f**	68[c]	>30:1
9	**5**	O[Si(*i*-Pr)$_2$]$_2$		-	**8**	75	10:1

[a] Isolated yield. [b] Determined by ^{1}H-NMR. [c] Reaction was carried out for 27 h.

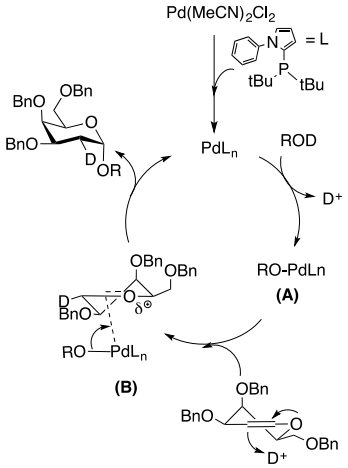
To probe the mechanism of our reaction, a 4:1 α:β-anomeric mixture of **3a** was subjected to the reaction conditions in the presence of acceptor **2a** and gave no change in the anomeric ratio, indicating that the high α-selectivity is not the result of anomerization (Figure S3, ESI). Reaction with deuterated galactal **9** yielded disaccharide **10** (90% yield) with the newly formed bonds *cis* to each other (Scheme 2A and Figure S1 in ESI). Moreover, glycosylation between galactal **1a** and CD_3OD yielded α-linked d3-methyl 2-d-glycoside **11**, in which deuterium from the nucleophile is incorporated equatorially at C-2, (Scheme 2B and Figure S2 in ESI). These results confirm the OH nucleophile as the H source and that both the C-H/D and the C-O bond formation steps are preferentially *syn*-diastereoselective. Moreover, addition of 1-phenylpyrrole or K_2CO_3 (0.3 equiv.) as exogenous bases, yielded only starting material, suggesting that sequestering acid generated during the reaction is detrimental to product formation.



Scheme 2. Mechanistic studies with glycal donors 9, 1a and 1g.

^{1}H-NMR spectroscopy studies in CD_2Cl_2 of mixtures of $Pd(MeCN)_2Cl_2$, ligand **L2** and glycoside donor **1a** did not show any changes in the spectra, while mixtures of $Pd(MeCN)_2Cl_2$ and **1a** in the absence of **L2** clearly showed downfield H-shifts associated with alkene protons in **1a** (from δ 6.37 ppm to 6.20 and 6.03 ppm), suggesting the presence of phosphine **L2** prevents the interaction between Pd and the glycal enol ether. Furthermore, NMR mixtures of $Pd(MeCN)_2Cl_2$, ligand **L2** and glycoside acceptor **2a** showed downfield shifts for the OH signal in **2a** from δ 1.86 ppm to 2.00 ppm, while no spectral changes were observed in NMR mixtures of **L2** and **2a** in the absence of Pd(II) (See ESI for details). Furthermore, glycosylation reactions between **1a** and cinnamyl alcohol **2j**, which bears a double bond or allyl-protected galactal **1g** and **2a**, proceeded smoothly to the corresponding α-glycosides **3j** (66 %) and **6g** (68 %) with excellent stereocontrol >30:1 α:β ratio (Scheme 2, C and D). These results further demonstrate that phosphine ligand **L2** is able to fine-tune the palladium reactivity towards alkoxypalladation, rather than palladium-mediated

activation of the alkene. NMR spectroscopy was then used to try to identify reaction intermediates from the glycosylation between **1a** and **2c** at 50 °C. Aliquots were taken from the reaction at different time points and the samples quenched by cooling to 0 °C prior to analysis.[9] Only anomeric signals (H and C) corresponding to starting material and product were observed (see Figures S6 and S7 in ESI), suggesting the reaction proceeds via short-lived intermediates.



Scheme 3. Proposed mechanism.

While a detailed mechanism awaits further investigation, our findings suggest, as proposed in Scheme 3, that in the presence *N*-phenyl-2-(di-tert-butylphosphino)-pyrrole **L2**,[9] palladium-catalyzed coupling of glycals with alcohol nucleophiles involves the initial insertion of Pd into the RO-H bond, rather than the traditional pathway of palladium-mediated alkene activation,[3] to produce alkoxypalladium species (A) with concomitant H^+ release from the OH nucleophile.[10] Proton catalysed glycal activation can now take place from the less hindered face, which leads to the formation of a transient oxocarbenium ion (B), although two diastereomeric half-chair conformers are possible, the depicted conformer (B) is favored[11], which quickly reacts with the activated oxygen nucleophile in (A) in a stereoselective manner to give the corresponding α-glycoside. This pathway is preferred due to sterics, the anomeric effect and a chair-like transition state, thus a low barrier is expected compared to competing pathways that would lead to the β-product.[12]

In conclusion, we have described the first example of a non-π-allyl mediated Pd-catalysed direct and stereoselective glycosylation of glycal enol ethers. This mechanistically interesting reaction is mild and widely applicable to a range of glycal donors and nucleophile acceptors, including some bearing alkene functionalities. The reaction proceeds with excellent yields and high selectivity for the α-anomer and is tolerant of most common protecting groups. We exemplify the generality and versatility of the approach in the stereoselective synthesis of a series of disaccharides, glycosyl-amino acids and other glycoconjugates. Given the abundance of chiral acetals in natural products, where alkene functionalities are also featured, this method might find applications in and beyond the field of carbohydrates.

Experimental Section

Experimental Details. The glycal donor **1**, **4**, **5** or **9** (~ 50 mg, 1.0 eq.), nucleophile acceptor **2** (0.75 eq.), $Pd(CH_3CN)_2Cl_2$ (0.25 eq.) and ligand **L** (0.3 eq.) were weighed into an oven dried microwave vial, sealed and placed under vacuum for 1 h. The vial was then filled with N_2 and ~ 1.0 ml anhydrous solvent (dichloromethane) was added. The mixtures were stirred and heated at 50 °C in the sealed vial until the reaction was determined to be complete by either TLC or NMR analysis of the crude material (Table 1 and 3 in manuscript for specific details). The reaction mixture was quenched by filtering through a celite bed and washed with additional solvent, then concentrated *in vacuo* and purified by column chromatography.

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Keywords: Pd (II) catalysis • deoxyglycosides • stereoselectivity • glycosylation • chiral acetals

(1) (a) X. M. He, H. W. Liu, Curr. Opin. Chem. Biol. **2002**, *6*, 590. (b) In Glycoscience: Chemistry and Chemical Biology; T. K. Lindhorst, Ed.; Springer: Berlin, **2001**.

(2) (a) E. I. Balmond, D. M. Coe, M. C. Galan, E. M. McGarrigle, Angew. Chem. Int. Ed. **2012**, *51*, 9152. (b) E. I. Balmond, M. C.Galan, E. McGarrigle, M. Synlett **2013**, *24*, 2335. (c) E. I. Balmond, D. Benito-Alifonso, D. M. Coe, R. W. Alder, E. M. McGarrigle, M. C. Galan, Angew. Chem. Int. Ed. **2014**, *53*, 8190. (d) S. Medina, M. J. Harper, E. I. Balmond, S. Miranda, E. M. G. Crisenza, D. M. Coe, E. M. McGarrigle, M. C. Galan, Org. Lett. **2016**, *18*, 4222. (e) S. Medina, M. C. Galan, Carbohydr. Chem. **2016**, *41*, 59. (f) C. Palo-Nieto, A. Sau, R. Williams and M. C. Galan. *J. Org. Chem.* **2017**, 82, 40.

(3) For recent reports: (a) K. N. Baryal, D. Y. Zhu, X. H. Li, J. L. Zhu, Angew. Chem. Int. Ed. **2013**, *52*, 8012. (b) M. Kaneko, S. B. Herzon, Org. Lett. **2014**, *16*, 2776. (c) T. K. Pradhan, C. C. Lin, K. K. T. Mong, Org. Lett. **2014**, *16*, 1474. (d) J. P. Issa, C. S. Bennett, J. Am. Chem. Soc. **2014**, *136*, 5740. (e) H. Wang, J. Y. Tao, X. P. Cai, W. Chen, Y. Q. Zhao, Y. Xu, W. Yao, J. Zeng, Q. Wan, Chem.-Eur. J. **2014**, *20*, 17319. (f) W. Z. Song, Y. Zhao, J. C. Lynch, H. Kim, W. P. Tang, Chem. Commun. **2015**, *51*, 17475. (g) S. Das, D. Pekel, J. M. Neudorfl, A. Berkessel, Angew. Chem. Int. Ed. **2015**, *54*, 12479. (h) R. S. Thombal, V. H. Jadhav, RSC Adv **2016**, *6*, 30846. (i) J. M. Nogueira, M. Bylsma, D. K. Bright, C. S. Bennett, Angew. Chem. Int. Ed. **2016**, *55*, 10088 (j) H. Tanaka, A. Yoshizawa, T. Takahashi, Angew. Chem. Int. Ed. **2007**, *46*, 2505. (k) V. P. Verma, C. C. Wang, Chem.-Eur. J. **2013**, *19*, 846. (l) D. Y. Zhu, S. Adhikari, K. N. Baryal, B. N. Abdullah, J. L. Zhu, J Carbohydr. Chem. **2014**, *33*, 438. (m) D. S. Liu, S. Sarrafpour, W. Guo, B. Goulart, C. S. Bennett, J.Carbohydr. Chem. **2014**, *33*, 423. (n) D. Y. Zhu, K. N. Baryal, S. Adhikari, J. L. Zhu, J. Am. Chem. Soc. **2014**, *136*, 3172. (o) T. M. Beale, P. J. Moon, M. S. Taylor, Org. Lett. **2014**, *16*, 3604.

(4) For recent literature: (a) Y. Li, X. Y. Yang, Y. P. Liu, C. S. Zhu, Y. Yang, B. Yu, B. Chem.-Eur. J. **2010**, *16*, 1871. (b) X. H. Li, J. L. Zhu, J Carbohydr. Chem. **2012**, *31*, 284 and references therein. (c) M. J. McKay, H. M. Nguyen, ACS Catal. **2012**, *2*, 1563 and references therein. (d) S. Adhikari, K. N. Baryal, D. Y. Zhu, H. Li, X. J. L. Zhu, ACS Catal **2013**, *3*, 57. (e) S. Medina, A. S. Henderson, J. F. Bower, M. C. Galan, Chem. Commun. **2015**, *51*, 8939. (f) P.

Peng, R. R. Schmidt, J. Am. Chem. Soc. **2015**, *137*, 12653. (g) R. Roy, A. K. Palanivel, A. Mallick, Y. D. Vankar, Eur. J. Org. Chem. **2015**, *18* 4000. (h) A. M. Vibhute, A. Dhaka, V. Athiyarath, K. M. Sureshan, Chem. Sci. **2016**, *7*, 4259. (i) R. S. Babu, Q. Chen, S. W. Kang, M. Q. Zhou, G. A. O'Doherty, J. Am. Chem. Soc. **2012**, *134*, 11952. (j) X. H. Li, J. L. Zhu, *Eur J Org Chem* **2016**, 4724.

(5) (a) T. V. Rajanbabu, *J. Org. Chem.* **1985**, *50*, 3642. (b) R. S. Babu, G. A. O'doherty, *J. Am. Chem. Soc.* **2003**, *125*, 12406. (c) A. C. Comely, R. Eelkema, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2003**, *125*, 8714. (d) H. Kim, H. Men, C. Lee, *J. Am. Chem. Soc*. **2004**, *126*, 1336.

(6) S. Boonyarattanakalin, X. Y. Liu, M. Michieletti, B. Lepenies, P. H. Seeberger, *J. Am. Chem. Soc.* **2008**, 130, 16791.

(7) B. D. Sherry, R. N. Loy, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4510.

(8) D. Hou, T.L. Lowary, *J. Org. Chem.* **2009**, *74*, 2278.

(9) The reaction does not proceed at room temperature and any potential long-live intermediates, if present, would be observed in this experiment.

(10) The reaction in the presence of **L2** and absence of Pd(II) does not proceed. (Table 1, entry 20).

(11) A hydroalkoxypalladation-type mechanism can not be completely discarded, however only starting material was observed when K_2CO_3 or 1-phenylpyrrole were added to the reaction, supporting an acid catalysed mechanism.

(12) M. Bols, X. Liang, H. H. Jensen, J. Org. Chem. 2002, 67, 8970.

(13) L. Ayala, C. G. Lucero, J. A. C. Romero, S. A. Tabacco, K. A. Woerpel, *J. Am. Chem. Soc.* **2003**, *125*, 15521.) C. M. Pedersen, L. G. Marinescu, M. Bols, *C. R. Chim.* **2011**, *14*, 17-43.

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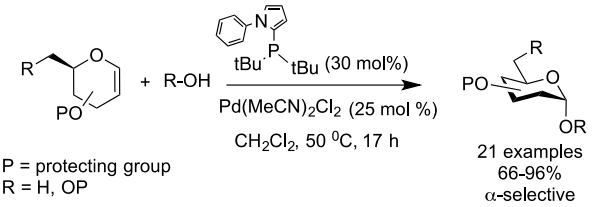
COMMUNICATION



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Palladium-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals.

Palladium (II) in combination with a monodentate phosphine ligand enables the unprecedented direct and α-stereoselective catalytic synthesis of deoxyglycosides from glycals. Mechanistic studies suggest that in the presence of *N*-phenyl-2-(di-tert-butylphosphino)pyrrole, the reaction proceeds via an alkoxy-palladium intermediate that increases the proton acidity and oxygen nucleophilicity of the alcohol.